

**The prognostic impact of different tumor marker levels in nonseminomatous germ cell tumor patients with intermediate prognosis: A registry of the International Global Germ Cell Tumor Collaborative Group (G3)**

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## HIGHLIGHTS

- Overall survival rates correlate with different AFP and LDH levels but not with HCG levels within the intermediate prognosis category according to IGCCCG.
- The majority of patients with intermediate prognosis and nonseminomatous histology expect a 5-year OS rate of ~89% which is almost similar to the good prognosis category.
- A small fraction of patients with LDH values >3 UNL and/or AFP > 6,000 IU/ml reflect a high risk population with impaired outcome. The optimal management of these patients warrants further investigations.

## ABSTRACT

### BACKGROUND

Germ cell tumor patients with intermediate prognosis (IPGCT) according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification represent a heterogeneous group with different clinical features. This analysis was performed to investigate the prognostic impact of different tumor marker levels prior to first line chemotherapy within IPGCT.

### METHODS

For this study an international registry for IPGCT was established. Eligibility criteria were intermediate prognosis according to IGCCCG criteria, nonseminomatous histology, male sex, and age  $\geq 16$  years. Uni- and multivariate analysis were conducted to identify characteristics associated with survival outcomes. Receiver-Operating-Characteristic curve analysis was applied to find cut-off parameters. Five-year overall survival (OS) rate was the primary and 5-year progression-free survival rate the secondary endpoint.

### RESULTS

This database included 634 IPGCT with a median follow-up of 9.0 years (interquartile range: 14.35). Patients received first line treatment with platinum based chemotherapy, associated with a 5-year OS rate of 87%. The stratification of patients according to AFP levels revealed a correlation between AFP levels and outcome, associated with 5-year OS rates of 88% for AFP levels <1,000 IU/ml (n = 303), 89% for 1,000 to 2,000 IU/ml (n = 82), 87% for >2,000 to 6,000 IU/ml (n = 121), and 82% for >6,000 IU/ml (n = 57) prior first course of chemotherapy, respectively (P=

0.013). LDH levels prior first course of chemotherapy also correlated with outcome associated with 5-year OS rates of 92% for  $<2$  UNL ( $n = 271$ ), 89% for  $\geq 2$  to 3 UNL ( $n = 85$ ), 78% for  $>3$  to 4 UNL ( $n = 34$ ), and 77% for  $>4$  UNL ( $n = 79$ ), respectively ( $P = 0.03$ ). Different HCG levels prior chemotherapy were not associated with outcome. In multivariable analysis AFP levels  $>6,000$  IU/ml ( $P = 0.023$ ; hazard ratio HR 2.263) or  $>1,982$  IU/ml ( $P = 0.031$ ; HR 1.722), and LDH levels  $>3$  UNL ( $P < 0.001$ ; HR 2.616) were independent prognosticators for OS.

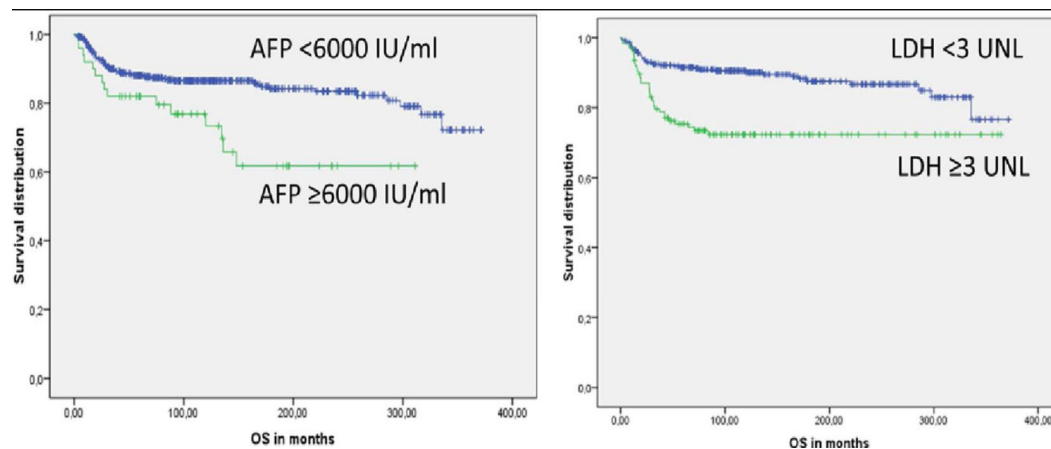
## CONCLUSIONS

Prognostication according to LDH and AFP levels prior chemotherapy could offer a new approach to stratify patients within the intermediate prognosis cohort. According to our findings, patients with AFP values above 6,000 IU/ml or/and LDH  $> 3$  UNL represent an independent high risk cohort.

Our results need to be confirmed in the upcoming IGCCCG reclassification.

*Keywords: AFP and LDH levels; IGCCCG classification; Intermediate prognosis; Risk factor stratification.*

## GRAPHIC ABSTRACT



## **1. INTRODUCTION**

The prognostic factor-based staging classification for patients with metastatic germ cell tumors (GCT), introduced in 1997 by the International Germ Cell Cancer Collaborative Group (IGCCCG) relies on data from the 1970s to 1980s [\[1\]](#). This system stratifies patients into good, intermediate, or poor prognosis categories based on different patient characteristics such as histology, tumor marker levels in case of nonseminomatous histology and metastatic sites at first diagnosis. The good, intermediate, and poor prognosis categories were initially associated with 5-year OS rates of 91%, 79%, and 48%, respectively and standard treatment for the intermediate and poor prognosis category has remained BEP with application of four cycles [\[2\]](#), [\[3\]](#), [\[4\]](#), [\[5\]](#). Nowadays, these data seems outdated as recent analyses suggest that outcome improved remarkably for each risk group over the last decades [\[6\]](#), [\[7\]](#), [\[8\]](#). Moreover, current analysis revealed no significant difference concerning the outcome between good and intermediate prognosis category, which further questions the applicability of the IGCCCG classification for GCT patients with intermediate prognosis (IPGCT) [\[6\]](#). Secondary, similar treatment approaches for intermediate- and poor prognosis patients may result in overtreatment for some IPGCT [\[9\]](#). Hence, the definition of clinical characteristics with prognostic impact within the intermediate prognosis category may assist to better estimate outcomes and could improve individual treatment decision-making based on a novel stratification system. As indicated in our previous works, AFP and LDH cut-off levels prior first line chemotherapy were prognosticators within IPGCT [\[8\]](#), [\[9\]](#). To examine the association between outcome and different tumor marker levels for IPGCT with nonseminomatous histology in more detail, a patient stratification system according to different tumor marker levels was established.

## **2. PATIENTS AND METHODS**

### **2.1. STUDY POPULATION**

Altogether 14 centers across Europe, the Russian Federation, USA and Australia participated, after initiation of this project within the global GCT collaborative group (G3). After approval by the local ethics committee, clinical information was collected retrospectively.

## **2.2. INCLUSION CRITERIA**

This analysis included nonseminomatous IPGCT according to the IGCCCG risk classification. Inclusion criteria were intermediate prognosis according to IGCCCG criteria, nonseminomatous histology, male sex, and age  $\geq 16$  years. Patients were first diagnosed and received treatment from 1980 to 2014.

## **2.3. STATISTICAL ANALYSIS**

It was the objective of this project to prove different marker levels to be associated with outcome and to test the correlation between rising tumor marker levels (AFP, LDH, and HCG), and prognosis within IPGCT with nonseminomatous histology. Primary end-point was the 5-year overall survival (OS) rate defined as the percentage of people in our population who are alive 5 years after their primary diagnosis or treatment initiation. Secondary endpoint was the 5-year progression-free survival (PFS), defined as the time from treatment initiation until disease progression or death due to disease. Patients lost to follow-up were censored at the date of last visit. The following patient characteristics were evaluated as potential prognostic factors: histology of the primary tumor, presence / absence of metastases to the following organs e.g., lymph node involvement, lung involvement, localization of the primary tumor (gonadal vs. extragonadal), AFP, HCG, and LDH levels prior first line of chemotherapy.

Calculation of correlations between subgroups was performed by  $\chi^2$  test. Survival analysis was conducted using the method of Kaplan-Meier [\[10\]](#). The log-rank test was applied to compare survival estimates, and multivariate Cox regression analysis was used in multivariate models. For patients characteristics that displayed a trend to be associated with OS and/or PFS with a  $P$  value of  $\leq 0.1$  multivariate analysis was performed to confirm these factors as independent prognosticators. Results were considered statistically significant with a two-sided  $P$  value  $< 0.05$ . Statistical analyses were conducted using SPSS software version 24.

## **3. RESULTS**

In total, 634 IPGCT with a median follow-up of 9.0 years (interquartile range [IQR]: 14.35) were eligible for this retrospective analysis. Patients were diagnosed from 1980 to 2014.

Altogether 107 patients were first diagnosed in the 1980s (17%), 140 patients in the 1990s (22%), and 387 patients were diagnosed since 2000 (61%).

### 3.1. CLINICAL CHARACTERISTICS

The median age was 31 years (range: 16–62). At first diagnosis, 246 (39%) patients were staged as UICC stage II A–C, and 368 (58%) as UICC stage III A–C, respectively. For 20 patients (3%) the exact stage was missing. Median levels of tumor markers prior chemotherapy were: AFP 700 IU/ml (IQR: 2,521; 25% percentile 33.4; 75% percentile 2,550), HCG 343 U/l (IQR: 4,978; 25% percentile 21.3; 75% percentile 5,000), and LDH 716 U/l (IQR: 861 25% percentile 397.5; 75% percentile 1,258.3). Altogether  $n = 303$  patients had AFP levels of <1,000 IU/ml. These patients were considered to be part of the intermediate prognosis category due to LDH levels >1.5 UN in 278 cases and/or elevated HCG levels with another 56 cases. Patient characteristics are reported in [Table 1](#).

**Table 1. Patient characteristics.**

Characteristics	Absolute number of patients $n = 634$	%
Primary testicular	585	92
Extragonadal retroperitoneal	48	8
Organ involvement:		
Lymph nodes	469	74
Lungs	198	31
Stage UICC:		
Ila–c	246	39
IIla–c	368	58
Not available	22	3
Years of first diagnosis:		
1980s	107	17

1990s	140	22
2000	387	61
Best response to first line:		
Responder (CR/PR-)	523	82
No change	14	2
Progressive disease	10	2
Not available	87	14
Secondary surgery after chemotherapy	226	36

### 3.2. TREATMENT

First-line chemotherapy was conducted according to the BEP regimen in 619 (98%) patients, including 6 patients treated with T (paclitaxel)-BEP and 3 patients receiving dose-intensification after 2 cycles BEP according to the SWENOTECA Protocol [11]. One patient received VIP (cisplatin, etoposide, and ifosfamide). In 8 patients (1%), the exact treatment regimen was not described. Patients received a median of 1 (range: 1-8) treatment line.: first line chemotherapy was performed with 4 cycles in 495 patients of platinum based chemotherapy; 45 patients received 3 cycles and 61 five to six cycles, respectively. Altogether 14 patients received less than 3 cycles.

Information concerning best response was available in 552 patients (87%). Of these, 185 patients (33%) achieved a complete remission defined as normal tumor marker levels and no radiological signs of disease  $\geq 1$ cm. With 338 patients (62%), the majority achieved a marker negative partial remission defined as normal tumor markers levels and a decrease of tumor masses  $\geq 30\%$  compared to baseline but with  $\geq 1$ cm residual masses. In 8 patients (1%), a marker positive partial remission was described defined as elevated tumor markers levels and residual disease with  $\geq 30\%$  decrease compared to baseline but with  $\geq 1$ cm residual masses. Furthermore stable disease/no change was described in 6 (1%) and progressive disease (PD) defined as increase of tumor markers levels (AFP or

HCG) after 2 sequential evaluations within 2 weeks; tumor growth or new lesions (growing teratoma syndrome excluded), occurred in 10 patients (2%).

Of the 338 patients with marker negative partial remission, 226 patients (67%) received secondary surgery and 112 patients (33%) underwent no further resections. The majority of the surgical interventions specified were lymphnode dissections of the retroperitoneum. Surgical procedures performed were as follows: lymphnode dissections of the retroperitoneum in 128 patients and/or, resection of lung metastases in 24 patients and/or, orchiectomy after chemotherapy in 5 patients. For 69 patients, the exact surgical intervention was not exactly specified.

By the comparison of treatment responders with versus without secondary surgery, the 5-year OS rate and of patients with vs. without secondary surgery was 85% vs. 86%, respectively ( $P= 0.364$ ). The 5-year PFS rate was 78% with secondary surgery vs. 55% without secondary surgery; respectively ( $P<0.001$ ).

Altogether 151 patients (25%) relapsed after first line treatment. These patients received further treatment lines. Patients with relapse received further treatment lines. Second line chemotherapy consisted of conventional dosed salvage regimens with VIP in 33 and TIP in 19 cases. In 6 cases, the name of second treatment line was unknown. In 14 cases, high dose chemotherapy with autologous stem cell transfusion was performed in the second line.

### **3.3. OUTCOME**

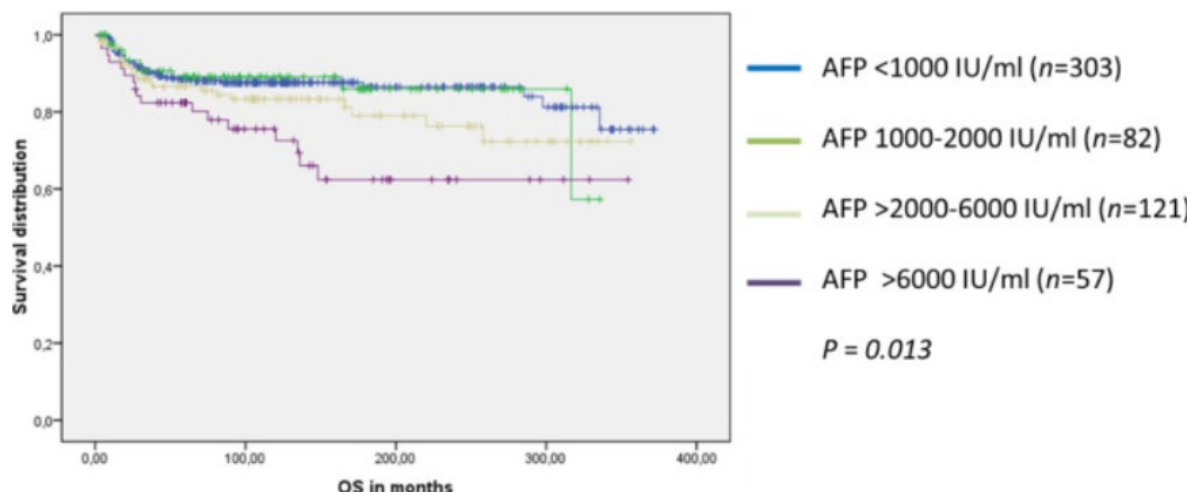
The 5-year OS and PFS rate was 87% and 81%, respectively. The 5-year OS survival rates stratified according to the time period of first diagnosis were 81% for patients diagnosed from 1980 to 1986, 85% for patients diagnosed from 1987 to 1996, 88% for patients diagnosed from 1997 to 2005, and 91% for patients diagnosed since 2006, respectively.

### **3.4. RISK FACTOR ANALYSIS FOR OS**

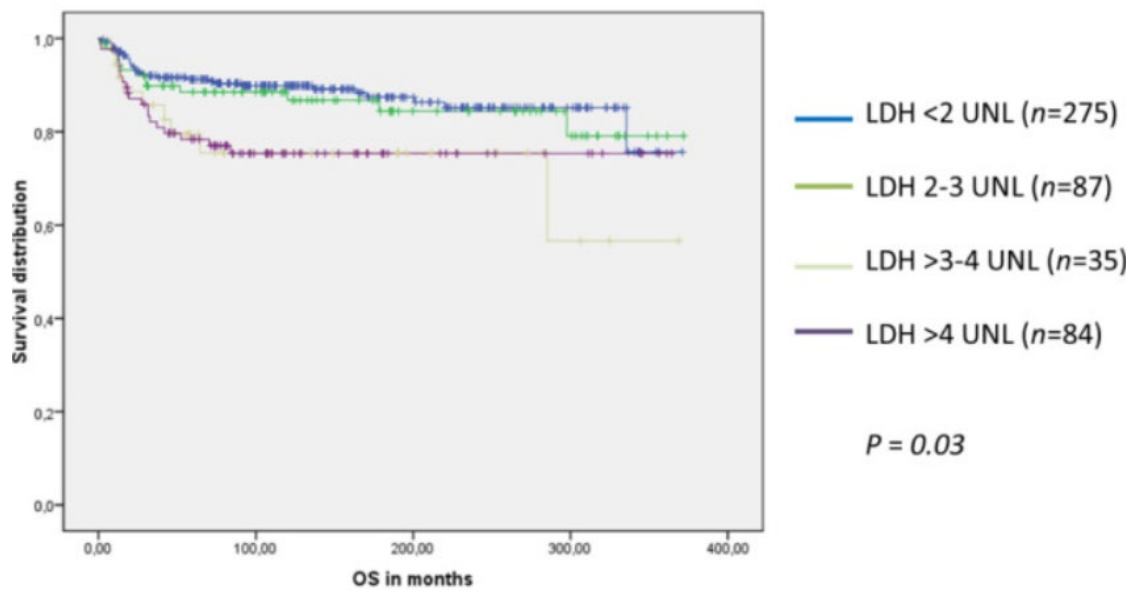
A stratification of patients according to AFP levels of <1,000 IU/ml ( $n = 303$ ), 1,000 to 2,000 IU/ml ( $n = 82$ ), >2,000 to 6,000 IU/ml ( $n = 121$ ), and >6,000 ( $n = 57$ ) IU/ml prior first



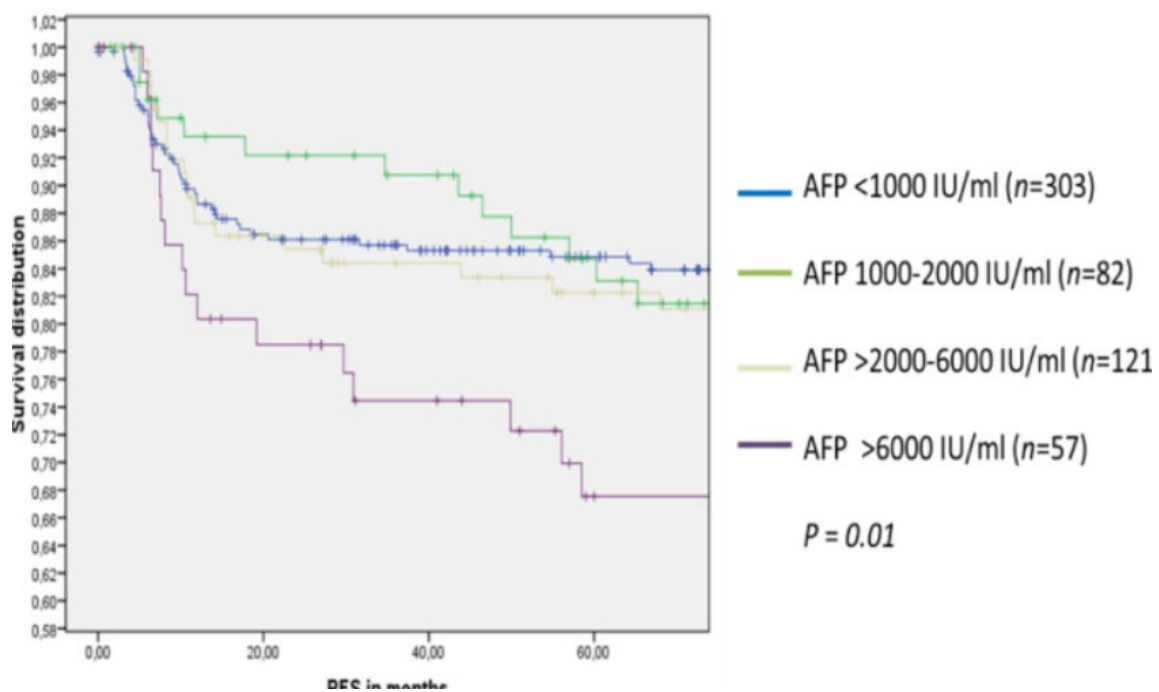
course of chemotherapy, revealed a correlation between AFP levels and outcome, associated with 5-year OS rates of 88%, 89%, 87%, and 82%, respectively ( $P= 0.013$ ) (Fig. 1). A patient stratification according to LDH levels  $<2$  UNL ( $n = 271$ ),  $\geq 2$  to 3 UNL (85),  $>3$  to 4 UNL ( $n = 34$ ), and  $>4$  UNL ( $n = 79$ ) prior chemotherapy also correlated with OS associated with 5-year OS rates of 92%, 89%, 78%, and 77%, respectively ( $P= 0.03$ ) (Fig. 2). In univariable analysis AFP levels  $>6,000$  IU/ml ( $P= 0.004$ ) and LDH levels  $>3$  UNL ( $P< 0.001$ ) correlated with an impaired OS. ROC curve analysis revealed the AFP value of 1,982 IU/ml as significant cutpoint concerning death events with a 5-year OS rate of 86% vs. 88% ( $P= 0.028$ ). Rising HCG levels did not correlate with outcome in this patient population (Fig. 4).



**Fig. 1.** OS of patients with intermediate prognosis according to initial AFP levels.



**Fig. 2.** OS of patients with intermediate prognosis according to initial LDH levels.



**Fig. 4.** PFS of patients with intermediate prognosis according to initial AFP levels.

In multivariable analysis AFP levels >6,000 IU/ml ( $P = 0.023$ ; HR 2.263) or >1,982 IU/ml ( $P = 0.031$ ; HR 1.722) and LDH levels >3 UNL ( $P < 0.001$ ; HR 2.161) were confirmed as independent prognosticators for OS (Table 2).

**Table 2. Results of univariate and multivariate analyses of PFS and OS.**

Factor	P value 5-year PFS		P value 5-year OS
LDH >3 UNL vs. LDH <3 UNL	0.659 (79% vs. 85%; 95% CI 262.3–293.7)		<0.001 (80% vs. 88%; 95% CI 301.2–325.6)
AFP >6,000 IU/ml vs. ≤6,000	<0.001 (70% vs. 84%; 259.7–288.8)		0.004 (92% vs. 88%; 95% CI 294.3–319.5)
Embryonal vs. nonembryonal	0.332 (80% vs.84%; 95% CI 259.7–289.6)		0.179 (86% vs. 90%; 95% CI 298–322)
HCG levels <5,000 vs. 5,000–1,000 vs. >1,000	0.439 (92% vs.73% vs.76%; 95% CI 198.1–232.5)		0.236 (88% vs. 82% vs.92%; 95% CI 280.5–212.3)
Chorion vs. nonchorion	0.815 (79% vs. 83%; 95% CI 260.3–290.2)		0.204 (83% vs. 90%; 95% CI 300.5–325.0)
UICC stage II vs. III	0.717 (81% vs. 82%; 95% CI 257.5–285.8)		0.249 (90% vs. 85%; 95% CI 296.1–320.0)
Lymphnode metastases vs. none	0.485 (81% vs.79%; 95% CI 260.3–289.4)		0.620 (89% vs. 87%; 95% CI 299.5–323.2)
Lung metastases vs. none	0.641 (81% vs. 82%; 95% CI 260.3–289.4)		0.671 (88% vs. 87%; 95% CI 299.5–323.2)
Teratoma vs. no teratoma	0.253 (73% vs.83%; 95% CI 161.1–179.7)		0.698 (90% vs. 92%; 95% CI 185.6–199.4)
Gonadal vs. extragonadal	0.202 (78% vs. 83%; 95% CI 257.7–285.7)		0.757 (87% vs. 86%; 95% CI 296.8–320.3)
Yolk sac vs. no yolk sac	0.797 (82% vs. 82%; 95% CI 261.1–290.9)		0.793 (87% vs. 88%; 95% CI 301.4–325.7)
	Results of multivariable Cox analyses of OS		
	Factor	OS (months)	
	HR	95% CI	P value
AFP level > 6,000 IU/ml	2.263	1.119–4.577	0.023

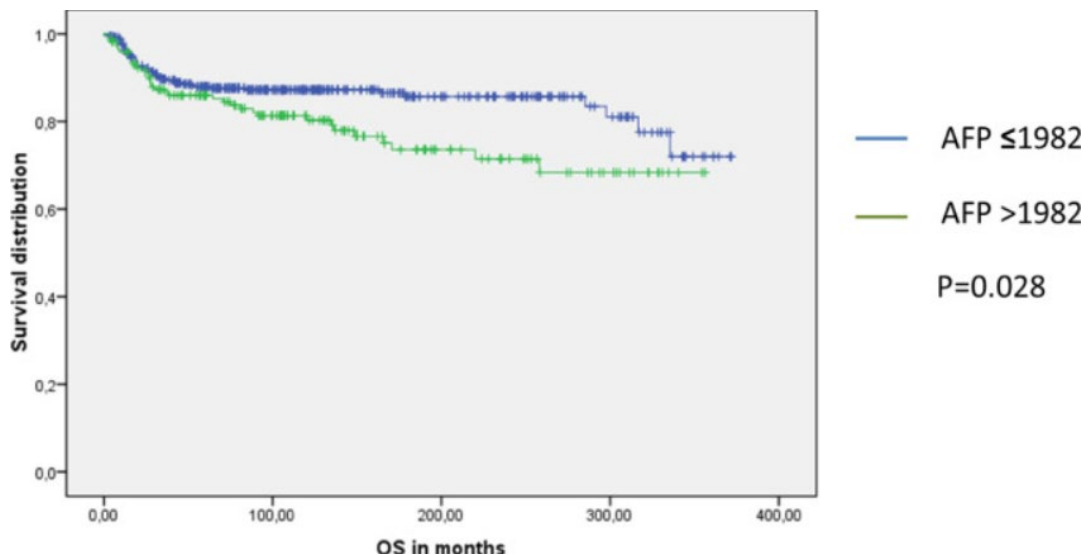
LDH > 3.0 UNL	2.616	1.621–4.221	<0.001
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Patients with AFP levels >1982 IU/ml had a higher risk of disease recurrence (recurrence rate: 20% vs. 31%;  $P= 0.02$ ) as did patients with LDH levels >2 UNL (recurrence rate: 29% vs. 42.5%;  $P= 0.047$ ).

The 5-year OS rate of patients with HCG levels from 0 to 5,000 U/l; 5,001 to 10,000 U/l and >10,000 U/l was 88%, 82%, and 91% ( $P= 0.236$ ).

### 3.5. RISK FACTOR ANALYSIS FOR PFS

The patient stratification according to AFP levels <1,000 IU/ml, 1,000 to 2,000 IU/ml, >2,000 to 6,000 IU/ml and >6,000 IU/ml prior first course of chemotherapy was also significantly correlated with the PFS, associated with 5-year PFS rates of 86%, 84%, 83%, and 68%, respectively ( $P= 0.01$ ) (Fig. 3). AFP cut-off value >6,000 IU/ml was also associated with an impaired 5-year PFS rate with 70% vs. 84% ( $P< 0.001$ ). LDH levels prior chemotherapy, did not correlate with PFS ( $P= 0.659$ ). Further results of statistical analysis are displayed in Table 2. There was no correlation with HCG levels stratified according to levels from 0 to 5,000 U/l; 5,001 to 10,000 U/l, and >10,000 U/l, and PFS ( $P= 0.439$ )



**Fig. 3.** AFP level of 1982 IU/mL as single cut-off variable concerning outcome.

#### 4. DISCUSSION

The IGCCCG classification reveals a heterogeneous cohort of patients with different histologic features and varying tumor marker levels before treatment initiation [2], [3], [4], [5]. Approximately 26% of the patients belong to the intermediate prognosis category. Defined by the presence of either AFP values of 1.000 to 10.000 IU/ml, HCG levels of 5.000 to 50.000 IU/l, LDH levels between 1.5 and 10 times the upper limit of normal range for nonseminomatous gonadal and retroperitoneal primary tumors, or the presence of nonpulmonary visceral metastases for those with pure seminoma, IPGCT represent a very heterogeneous cohort. While AFP and LDH cut-off values were previously described to be associated with OS [8], [9], this analysis was performed to characterize the prognostic impact of different LDH and AFP levels and tumor marker constellations prior first line chemotherapy. In our analysis, a 5-year OS rate of 87% could be achieved, which is superior to the description of previous IGCCCG data. Improved outcome of GCT patients was already reported within other studies [11], [12], [13]. We suppose that outcomes of advanced GCT patients significantly improved over the last decades, due to improved treatment conditions including dose density, better supportive care, and salvage treatment options for relapsed disease.

As outcome of IPGCT was currently described to be equivalent to the good prognosis category, the actuality and reliability of the IGCCCG-defined IPGCT category becomes questionable. Consequently, the implementation of new prognosticators could help to realize treatment decision based on individual risk factor assessment. In this analysis we found a correlation between rising marker levels and impaired outcome concerning OS for different LDH and AFP values. Here patients with AFP values >6,000 IU/ml and LDH > 3 UNL revealed an outcome similar to the poor prognosis category and therefore differ greatly from other IPGCT.

Our results demonstrate that the intermediate prognosis category represents a heterogeneous cohort according to different prognosticators. For patients with high marker levels, further investigations concerning optimal treatment strategies are needed.

Our analysis has several limitations due to its' retrospective design including partially missing data, and tumor marker levels edited by different laboratories around the world.

Further sources of error are a patient cohort treated in a time period of almost 40 years, as well as treatment performed in different parts of the world with different health systems. Central review concerning tumor markers and histology was not performed.

Nonetheless, we think that our data can provide reliable information for the optimal risk factor stratification for IPGCT which can depend on different LDH and AFP values.

We expect that the EORTC-led IGCCCG update initiative to give us further information how to deal with different marker constellation within different prognostic groups.

Furthermore, new approaches such as miRNAs as novel tumor markers for GCT patients will hopefully improve diagnosis, risk stratification, and treatment of GCT patients [\[14\]](#).

## **5. CONCLUSIONS**

Prognostication according to LDH and AFP levels prior chemotherapy may offer a new approach to stratify the heterogeneous group of nonseminomatous IPGCT. The largest fraction of our patients had AFP levels <6,000 IU/ml and LDH < 3 UNL associated with an outcome similar to those in the good prognosis, while patients with tumor marker levels >6,000 IU/ml and/or >3 UNL display a high risk group. The optimal treatment of these patients warrants further investigations. Our results need to be confirmed in the upcoming IGCCCG reclassification.

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